Pharmacology of Abused Drugs-2 :

Nicotine, Barbiturates, Benzodiazepines, Hallucinogens, PCP/Ketamine

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Today's Topics

- **Review of Last Week's Topics**
- **Pharmacokinetics and Pharmacodynamics of Additional Drug Classes**
- **Today: Nicotine, Barbiturates, Benzodiazepines, Hallucinogens, PCP/Ketamine**

Review: Drug Pharmacokinetics

- **Absorption depends on route, drug and affects % entering and rate of rise of blood (tissue)**
- **Distribution depends on blood flow and fat content**
- **Metabolism can activate or deactivate drugs**
- **Clearance is via liver/GI and kidney/urine routes**
- **Individual differences in metabolism**

PHARMACODYNAMICS: HOW DRUGS ACT ON CELLS & ORGANS

- **Most act by binding to specific receptor, usually on cell surface membrane**
- **Occasionally this has direct effects on neuron firing rate**
- **Most often, this produces more delayed effects, involving a change of small intracellular messenger molecules such as cGMP, followed by changes in enzymes and modification of regulatory proteins (and sometimes receptors), followed by change of cell gene expression, producing long-term effects**
- **Organ effects depend on distribution of cells with receptors as well as competing receptors and effects of receptor binding in particular cell types in particular organs**
- **Effects can be short- and long-term and this system is identical to systems for action of hormones and normal neurotransmitters**

Drug Abuse Pharmacology: Summary

- **Dose, drug, route, and metabolism affect drug blood and tissue levels**
- **Binding to specific receptor starts intracellular chain of events, producing specific effects similar to those produced by natural ligands**
- **Chronic exposure and genetics alter individual responses to drugs and dependence symptoms**
- **Reinforcement pathways involving DA critical to repetitive drug use**

Opiates

many drugs, therapeutic effect, oral and IV and transmucosal routes

good absorption, some activation

half lives affect duration of action and onset withdrawal

mu and delta and kappa receptors account for different effects; each has endogenous agonists

Reward and withdrawal involve different brain cell regions

Cannabis & Cannabinoids

THC major cannabinoid but multiple other compounds

Well-absorbed, fat soluble, very slow elimination

CB1 (CNS)and 2 (immune) receptors have different effects, with endogenous agonists

Cocaine

Many routes of absorption, including smoked, with rapid brain distribution and binding to DAT receptor

Metabolism to BE with elimination over days

Local anesthetic, reinforcing, sensitizing, with binge pattern of use and little or no withdrawal

Amphetamines

Many routes, most with good absorption [but sometimes delayed in pills] and rapid distribution to brain; rapid metabolism

Releases DA and inhibits DAT--> increased DA

Reinforces, acts in cortex too

Tolerance develops

Sensitization develops

No clear withdrawal

Nicotine Pharmacokinetics

- Many compounds in tobacco
- Burned tobacco has even more compounds, including CO, variou carcinogenic aryl hydrocarbons (tars), and nicotine
- Poor GI absorption after oral dosing
- Well-absorbed via transmucosal (oral, nasal), transdermal, and ora routes: these are most common routes of administration and of therapeutic substitution
- Rapid distribution in CNS, vasculature, other organs
- Rapid metabolism from nicotine to cotinine, which has longer half life

Nicotinic Receptors: Types and Binding Agents

- Present in invertebrates and all vertebrate species
- Natural agonist is acetylcholine, a common neurotransmitter in CNS and especially in PNS and at neuromuscular junction of vertebrates and invertebrates
- One of two cholinergic receptor types: other is muscarinic (named for binding of products of toxic, hallucinogenic mushroom *Amanita Muscaria)*
- Among the first receptors to have been purified, crystallized, and to have its gene cloned
- Many antagonists available, but little use for us

Nicotine Effects

- Increases DA release in N. Accumbens and inhibits COMT, the major DA catabolic (breakdown) enzyme in those neurons→ increases DA activity→ reinforces use
- Vasoconstriction (mild)→ coronary spasm, other vascular spasm, hypertension, Raynaud's
- Peripheral vasodilation (seen in patch use)
- Produces increase in heart rate
- Many cigarette and tobacco effects are NOT due to nicotine, but to the CO and tars, e.g., carcinogenesis, COPD

Nicotine tolerance & withdrawal

- Can develop after fewer than 1000 doses, but usually after prolonged use
- Onset, duration related to nic receptor dissociation rate
- Unclear if protracted abstinence occurs and is separate from depression
- Withdrawal associated with increased release of norepinephrine and epinephrine from CNS (locus coeruleus in brainstem) and periphery, SLOWED heart rate, tremor, insomnia, dysphoria, and irritability.
- Marked individual differences in withdrawal kinetics
- Tolerance and withdrawal have primarily intracellular mechanisms
- High rates of depression (F>>M)→ relapses

Nicotine withdrawal treatment

- Duration typically days-weeks, with 3 or 4 patterns (severe & prolonged, rapid decline, steady decline, delayed decline)
- Substitute pure nicotine for tobacco
- Transdermal patch, transmucosal (nasal inhaler, gum), pulmonary (inhaler) delivery systems all approved
- Given disturbance in DA-based reinforcement pathways, craving, anhedonia, and dysphoria common despite substitution
- Agents that modify this disturbance reduce relapse rates, e.g., bupropion (weak DA agent), nortriptyline and desipramine, SSRIs
- Combination appears to have highest success rates

Barbiturate and Benzodiazepine Pharmacokinetics

- Variably absorbed via oral, transmucosal (e.g., rectal phenobarbital), and intramuscular (e.g., diazepam poorly, lorazepam highly) routes
- Not volatile→ little pulmonary use
- Widely distributed in CNS, with high binding in cortex, amygdala, basal ganglia, spinal cord
- Many therapeutic uses, including treatment of epilepsy, sedation for invasive procedures, pain, anxiety, acute dystonia, and others
- Typical routes are oral and IV, and rarely are they smoked, injecte SQ, or snorted
- Complex metabolism

Barbiturate and Benzodiazepine Metabolism

- Mostly in liver
- Barb→delayed hepatic CYP450 activation→ shortens half-life of barbs, some other drugs
- This accounts for some metabolic tolerance
- Some genetic influences
- Some barbiturates and benzodiazepines are metabolized to active compounds, e.g., temazepam to oxazepam
- Half lives of barbiturates and benzodiazepines vary widely, from minutes (Brevital, midazolam) to several hours (phenobarbital, clonazepam)
- Many active metabolites have half lives of several days e.g., desmethyldiazepam, a diazepam (Valium) metabolite
- Increased half life of many benzodiazepines with age (flurazepam [Dalmane] 2-5 days)→ accumulation and toxicity
- In general, elimination is via conjugation and excretion in bile/urin

Barbiturate and Benzodiazepine (BZ) Receptors

- Lie on separate subunits of complex associated with GABA receptor and fast chloride channel, a membrane complex
- GABA is major inhibitory neurotransmitter in CNS
- Purified, crystallized, genes cloned
- Binding of barb or BZ changes shape of complex→increased GABA effect→increased chloride influx→ hyperpolarization of membrane→ inhibition of firing rate
- Genes evolutionarily conserved & present in most vertebrates—little genetic variation
- Natural benzodiazepine agonist discovered
- BZ antagonists bind with high affinity, displacing BZ→ useful in reversing overdose **(flumazenil)**
- Mechanism of dynamic tolerance not well characterized
- BZ receptors widely distributed in cortex, basal ganglia, amygdala brainstem, spinal cord

Barbiturate and Benzodiazepine (BZ) Effects

BZ and barbituratesproduce 9 major therapeutic/toxic CNS effects in dose-related manner

- **reinforcement (not highly potent, VTA-NAcc)**
- **reduction in anxiety and dysphoria**
- **motor slowing/incoordination (cerebellum, basal ganglia)***
- **muscle relaxation (basal ganglia, spinal cord)**
- **memory impairment (hippocampus)**
- **anti-epileptic effects (cortex, thalamus)**
- **respiratory depression (cortex, medulla)**
- **sedation (cortex, brainstem)**

***at low dose, motor activation is noted, as with EtOH**

Tolerance can be marked

Withdrawal syndrome is similar to alcohol withdrawal, but with higher seizure risk and time course of variable length, depending on rate of dissociation of drug from receptor

Hallucinogen Pharmacokinetics

- Hallucinogens are a very heterogeneous class, ranging from classic hallucinogens (LSD, DMT, mescaline, DMT, MDA, psilocin) to antimuscarinics (trihexphenidyl, Datura) to amphetamines and methcathinone (CAT), to a broad variety of others
- Classic hallucinogens are indoleamines (similar to serotonin, a neurotransmitter) and phenylalkylamines
- We will focus on classic hallucinogens, e.g. LSD
- Distribution primarily to CNS given high lipid solubility
- Metabolism variable, primarily in liver, with excretion in bile and urine
- Typical routes are oral, smoked, and IV (uncommon)

LSD and Classic Hallucinogen Pharmacodynamics

- Appear to act as agonists at serotonin (primarily $5HT_{2A}$) receptors
- Animals can reliably discriminate hallucinogens from saline and THC and amphetamine (but not other hallucinogens)
- VTA-Nacc system not activated and self-administration difficult to establish with hallucinogens
- No clear tolerance or withdrawal
- Some, such as methcathinone (CAT), also are CNS stimulants and increase movement, and are self-administered

Phencyclidine (PCP) & Ketamine (Special K): Pharmacology

- **Pharmacokinetic issues: use via oral/GI, pulmonary (PCP), and IV routes, with good distribution to CNS and muscle and fairly rapid elimination (PCP half life > ketamine)**
- **Therapeutic uses for ketamine as veterinary and pediatric anesthetic, producing dissociative state with potent pain relief**
- **In humans, intoxication associated with disinhibition, violence (PCP>>ketamine), sedation, rotatory nystagmus**
- **Appear to bind to sigma opiate receptor sites, for which there are natural agonists, located in spinal cord, brainstem, and basal ganglia as well as cortex**
- **No clear tolerance or withdrawal syndromes**

Summary-part 1

- **Pharmacology of action of substance of abuse is similar to normal action of normal hormones & neurotransmitters, as well as of therapeutic drugs**
- **Study of drug pharmacokinetics reveals much about drug effects, especially blood and urine levels**
- **Study of drug pharmacodynamics reveals action at specific receptors, often with natural agonists made by normal brain, and explains tolerance and withdrawal in some cases**

Summary-part 2

- **Nicotine acts at nicotinic cholinergic receptor, is well-absorbed transmucosally and in pulmonary tissue, and acts at DA pathway and elsewhere in CNS, with prolonged withdrawal syndrome that is Rx-responsive**
- **Sedatives such as barbiturates & BZ have variable, route-specific absorption, are sometimes activated metabolically, have complex effects on liver metabolism, act at GABA-Cl channel complex, and produce withdrawal with high risk seizures**
- **Hallucinogens are heterogeneous, and classic ones act at 5HT2A receptor, not DA pathway, and do not produce tolerance or withdrawal**
- **PCP & ketamine act at sigma opiate receptors, producing intoxication with dissociative analgesia**